

A Confront on Antiretrovirals in HIV Therapy

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Abstract

HIV belongs to retrovirus family and causes a chronic and deadly disorder named AIDS (Acquired Immuno Deficiency Disorder). Due to its complicated structure and lifestyle, discovery of a vaccine for its prevention has always been difficult. Over past few years, several drugs have been discovered in action against AIDS. Antiretrovirals are mainly used as drugs for medication which include Nucleoside Reverse Transcriptase Inhibitors (NRTI's); Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI's); and Fusion Inhibitors (FI). These are termed "Highly Active Antiretroviral Therapy" (HAART). Despite the fact that HAART treatment had an intense impact on AIDS epidemic, it carries its own drawbacks which include the adverse side effects associated with the therapy. Present article mainly focuses on different types of drugs which are administered in HAART, their classification, and side effects.

Introduction

Even though there were many antiviral drugs being synthesized in the recent past, still the search for potent antiviral agents is in pace to get rid of viral diseases [1]. With regard to the increasing number of viral infections, the development of different approaches to counteract these infections by introducing new therapeutic and prophylactic measures is widely accepted [2]. Beliefs about health and illness, in particular about the necessity of medication towards the illness and concerns about its potential adverse events, have been found to be influential in both HIV and other disease areas [3]. Prophylactic therapeutics and vaccines continue to be critical strategies to fight the spread of viral infections [4]. In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery. The estimated number of children under the age of 15 years living with this virus globally is 2.3 million as of 2005 [5,6]. At present a new approach is being tried to understand how disease and infection are controlled at the molecular and physiological level and to target specific entities based on this knowledge [7]. Some examples of such infections which are of concern now-a-days are, Dengue fever, Hepatitis B, HIV-AIDS, Pneumonia, Porcine reproductive and respiratory syndrome (PRRS), a re-emerging disease in swine, Influenza virus, West Nile virus, swine flu H1N1 virus [8-17]. Disseminated histoplasmosis is associated with Acquired Immunodeficiency Syndrome (AIDS), involves different organ systems and may be fatal if untreated [18]. The AIDS virus is a neurotropic virus and CNS involvement as the presenting complaint is seen in approximately 10% of cases of HIV infection [19]. Rhabdomyolysis, Histoplasmosis, tuberculosis, etc are examples of some diseases which are caused after the infection with HIV [20-22].

Some viruses prove to be fatal which have no vaccine or protective therapy available like Hendra and Nipah viruses [23] for which still research is going on for the production of antiviral therapies. While there is ample of literature on HIV occurrence among drug-using populations, few studies have investigated drug users' recent risky drug use and sexual behaviours, which are indicators for new HIV infection [24].

This article mainly focuses on the antiviral therapy, and its side effects for the treatment of the deadly Human Immuno Virus which causes Acquired Immuno Deficiency Syndrome (AIDS).

HIV-AIDS

Human immunodeficiency virus (HIV) is a member of the retrovirus family that causes acquired immunodeficiency syndrome (AIDS). It is a condition in humans in which progressive failure of the immune system is observed, which leads to life-threatening opportunistic infections and cancers to thrive. Infection with HIV occurs by various means like, transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. HIV is present as both free virus particles and virus within infected immune cells in these body fluids [5]. Unlike most bacteria, HIV particles are much too small to be seen through an ordinary microscope. However they can be seen clearly with an electron microscope.

Replication of HIV-1 is a complex process that is accomplished by various structural and non-structural viral proteins [25]. HIV particles surround themselves with a coat of fatty material known as the viral envelope (or membrane). Projecting from this are around 72 little spikes, which are formed from the proteins gp120 and gp41. Just below the viral envelope is a layer called the matrix, which is made from the protein p17 (Figure 1).

Currently, there are around 60 million people worldwide and in fact a staggering 16,000 new HIV infections reported daily. Several factors have contributed to increased rate of HIV infection across the world, most notably, unprotected heterosexual contact [26].

Pathogenesis

The Human immunodeficiency virus is made up of Genetic material, which is RNA, Chemicals like enzymes, and a protein coating. The RNA and enzymes help the virus enter and use other cells to make copies of itself. HIV mainly infects immune cells called T-lymphocyte cells (T-cells) [27]. HIV-1 infection is characterized by an insidious

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deterioration of the cellular immune system. Both the quantity and proportion of CD4+ T-cells in plasma decrease steadily over a period of years to decades, and leads to the development of acquired immunodeficiency syndrome (AIDS) in infected individuals. The pace at which immunosuppression develops also closely reflect the levels of HIV-1 RNA in plasma. Higher the HIV-1 viral load, greater the loss of circulating CD4+ T-cells per year. Gradually, the individual becomes immunocompromised, which leads to the infection of further more viruses, like, Human cytomegalovirus (HCMV) [28,29],

According to a case report, a previously asymptomatic man who presented with common, non-specific symptoms was diagnosed with a rare complication of non-typhi Salmonella infection. Further investigations exposed the presence of advanced HIV infection and with successive follow up a number of co-existing pathologies were diagnosed with fatal consequences [30].

Accurate quantification of HIV-1 Viral Load (VL) in plasma compartment is vital for disease monitoring and management which are carries out by Abbott m2000 and Roche COBAS TaqMan Methods [97].

Following are the steps of HIV infection [27] (Figure 2).

Human retroviruses are of following types,

- Human T cell leukemia viruses
 - HTLV-1
 - HTLV-2
- Human immunodeficiency virus
 - HIV-1
 - HIV-2

HTLV-1 and HTLV-2 belong to the subclass of oncovirinae and cause adult T cell leukemia and spastic paraparesis. HIV-1 and HIV-2 from the subclass lentivirinae are responsible for causing acquired immunodeficiency syndrome (AIDS)

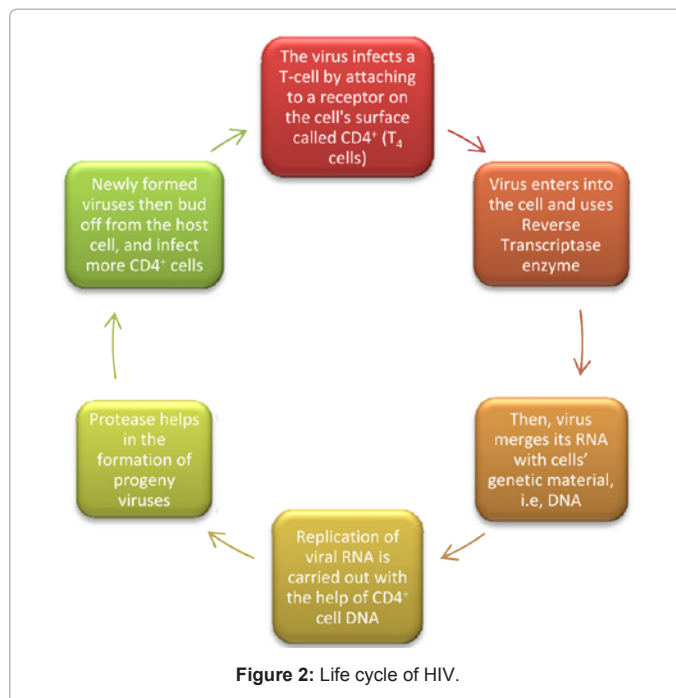


Figure 2: Life cycle of HIV.

Diagnosis

The primary tests for diagnosing HIV and AIDS include [31-36]

- ELISA (Enzyme Linked Immuno Sorbent Assay)
- Home Tests
- Saliva Tests
- Viral load tests
- Western blot

Present review focuses on a range of recent implications developed in the treatment of AIDS and also various side effects involved in the administration of these drugs.

HIV-AIDS Treatment

With regard to the rising number of zoonotic infections, the development of strategies to counteract OPV infections by introducing new therapeutic and prophylactic measures is widely accepted [37]. So far, there is no cure for HIV-AIDS, but medications are effective in fighting HIV and its complications. Special treatments are designed to reduce HIV in the body, keep your immune system as healthy as possible and decrease the complications that you may develop [38].

AIDS medications

HIV infection is a leading health crisis across the entire world, including United States. Recent advances in medicine have led to a considerable decline in mortality associated with HIV infection, thereby increasing the life expectancy of HIV-infected patients [39]. The CD4+ T-cell lymphocyte count (henceforth CD4+ count) is one of the most chief prognostic factors for development of HIV infection, and forms the basis for international recommendations for antiretroviral treatment and prophylaxis [40].

Even though there is no cure for acquired immunodeficiency syndrome (AIDS), medications have been formulated which have

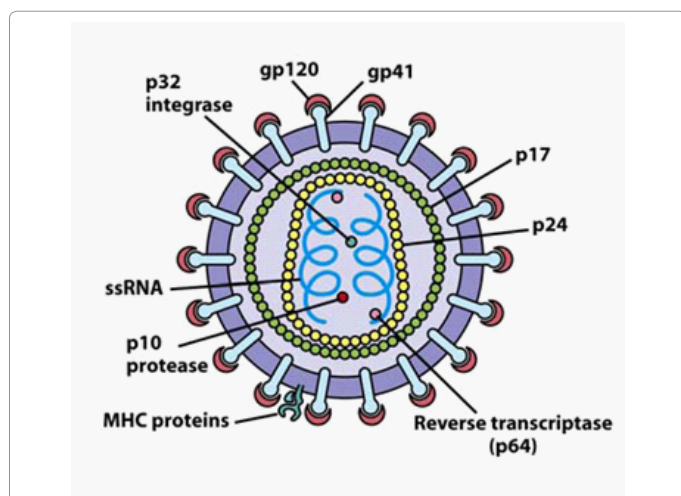


Figure 1: Structure of HIV. (Source: Thomas K. Kuby. "Immunology." New York: W.H. Freeman and Company; 2007).

proven to be highly effective in fighting HIV and its complications. Drug treatments like antivirals [41] help reduce the HIV in the body, keep the immune system as healthy as possible and decrease the complications one may develop [38]. Fifteen years after highly active antiretroviral therapy (HAART) became the standard of care in HIV infection, a few issues regarding the immunological effects of such therapy have been clarified, but still many points remain incompletely understood [42]. The different anti-HIV drugs which are available today are of three main types: NRTIs, NNRTIs and PIs. However, HIV Entry Inhibitors are being a key attention. Recently acquired knowledge about the process of entry of HIV, points to new approach to block the entry of virus.

For most HIV strains, infection of their target cells is mainly dependent on the presence of the CD4 receptors on the surface of the cells, which serves as the primary virus receptor. The attachment of the viral envelope to this cellular CD4 receptor can be considered as an ideal target with multiple windows of opportunity for therapeutic intervention. Therefore, drugs that interfere with the CD4 receptor, and thereby inhibiting viral entry, can be promising agents for the treatment of AIDS. Ligands that bind selectively to proteins of the membrane fusion pathway can retard or block viral entry [43]. The CD4-targeted HIV entry inhibitors Cyclotriazadisulfonamides represent a novel class of small molecule antiviral agents with a unique mode of action [44].

Nowadays Human Immunodeficiency Virus (HIV) is considered as a chronic disease because individuals have the potential to live upward of 20 years on highly active antiretroviral therapy [45]. The substantial success of antiretroviral drugs in reducing death rates by 50-80% over one decade makes HIV a manageable chronic illness [46]. Chemotherapy is mainly followed for the treatment of AIDS. These drugs are classified into mainly 4 categories based on the mode of action (Table 1).

Sometimes, HIV can even gain resistance to the antiretroviral drugs, thereby, making it even more complicated to cure the disorder. Emergence of HIV-1 drug resistance is at times an inevitable and anticipated consequence of antiretroviral therapy (ART) failure [47]. Most patients experience an excellent response to NNRTI containing treatment; however, a subset of individuals react poorly with slow virologic suppression and immunologic recovery, due to the rapid development of drug resistance [48].

Nucleoside reverse transcriptase inhibitors (NRTI): These drugs interrupt the virus from replicating, which slows the spread of HIV in the body. Combinations of NRTIs make it possible to take minimize the doses and maintain effectiveness. These drugs include [49].

- Combivir (Zidovudine and Lamivudine),
- Trizivir (Zidovudine, Lamivudine and Abacavir)
- Epzicom (Abacavir and Lamivudine) and
- Truvada (Tenofovir and Lamivudine).

Protease inhibitors (PI): These FDA-approved drugs interrupt virus replication at a later step in the virus life cycle. Since the introduction of protease inhibitors (PI) in highly active antiretroviral therapy (HAART) for HIV infection in the mid-1990s, HIV-related morbidity/mortality has decreased to one-fifteenth the level observed preceding to the HAART era [50].

Fusion inhibitors: Fusion inhibitors are a novel class of drugs that act against HIV by preventing the virus from fusing with the inside of a cell, preventing it from replicating. The group of drugs includes Enfuvirtide, also known as Fuzeon or T-20.

Non-Nucleoside reverse transcriptase inhibitors (NNRTI): Non-nucleoside reverse transcriptase inhibitors (NNRTIs) obstruct the infection of new cells by the virus. These drugs may be prescribed in combination with other anti-retroviral drugs.

Highly active antiretroviral therapy (HAART): Highly active antiretroviral therapy (HAART) was introduced in 1996 for people with HIV and AIDS. HAART (often referred to as the anti-HIV “cocktail”) is a combination of three or more drugs, such as protease inhibitors and other anti-retroviral medications. The treatment is highly efficient in decreasing the rate at which the HIV virus replicates itself, which may slow the spread of HIV in the body. The goal of HAART is to reduce the amount of virus load in the body, or the viral load, to a level that can no longer be detected in blood tests [49]. Enfuvirtide, a 36-amino acid synthetic peptide, is the first antiretroviral drug that inhibits the entry of HIV-1 into host CD4 lymphocytes [51].

Side effects associated with anti retroviral treatment

Side effects are symptoms or complications you may have when you take a medication. Almost all drugs which are used in the treatment of range of illnesses can cause side effects. HIV medications can also cause different reactions and make the patient feel sick. Most side effects one can see and feel, like headaches, upset stomach, nervousness, or trouble concentrating. But one might not be aware of some physical side effects, like liver or kidney damage [52]. In recent years particular awareness has been drawn to the effect of antiretroviral (ARV) therapies on the prevalence of serious non-AIDS events (SNAEs), including cardiovascular disease (CVD), end-stage renal disease, liver failure and fractures [53].

S.No	Nucleoside Reverse Transcriptase Inhibitors	Protease Inhibitors (PI)	Fusion Inhibitors	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
1	Abacavir (Ziagen, ABC)	Amprenavir (Agenerase, APV)	Enfuvirtide	Delvardine (Rescriptor, DLV)
2	Didanosine (Videx, dideoxyinosine, ddi)	Atazanavir (Reyataz, ATV)		Efravirenz (Sustiva, EFV)
3	Emtricitabine (Emtriva, FTC)	Fosamprenavir (Lexiva, FOS)		Nevirapine (Viramune, NVP)
4	Lamivudine (EpiVir, 3TC)	Indinavir (Crixivan, IDV)		
5	Stavudine (Zerit, d4T)	Lopinavir (Kaletra, LPV/r)		
6	Tenofovir (Viread, TDF)	Ritonavir (Norvir, RIT)		
7	Zalcitabine (Hivid, ddC)	Saquinavir (Fortovase, Invirase, SQV)		
8	Zidovudine (Retrovir, ZDV or AZT)			

Table 1: Types of drugs.

In this article, some examples of serious side effects and their impact on health of the individual are discussed.

Side effects for the different classes of drugs are discussed in (Table 2-4).

Some side effects are very common and will occur to most of the people administered with the drug. Other side effects are very uncommon. Age, body weight and size, gender, and overall health play an important role in onset of side effects [52]. These side effects range from mild disturbances in health to life threatening health disorders.

Highly active antiretroviral therapy, a combination of at least three drugs for HIV-1 infection has led to significant decrease in morbidity and mortality, and many HAART course of therapy resulted in near-complete suppression of HIV-1 replication. HAART is now the standard-of-care therapy. The substantial success of antiretroviral drugs in reducing death rates by 50-80% over one decade makes HIV a manageable chronic illness. The distribution of antiretroviral drugs has coincided with a dramatic drop in the number of officially reported AIDS deaths [69]. ENF is the first member of a class of antiretroviral drugs, termed entry inhibitors, recently joined by the CCR5 inhibitor maraviroc [70].

In tropical areas, one of the most well-known features of HIV infection is its frequent association with opportunistic or not often parasitical infectious diseases. These co-infections can have an influence in the intensity of HIV infection in particular in viral load and CD4 T-cell rate [75]. Treatment containing protease inhibitors (PI) are less commonly used in developing countries due to high cost and less availability [76].

Use of combination antiretroviral (ARV) therapy (cART), also referred to as highly active ARV therapy (HAART), has resulted in a noticeable advancement in the prognosis of HIV disease. In HIV-infected patients naïve to ARV therapy, treatment guiding principles suggest three drug regimens, most often including a boosted protease inhibitor (PI/r) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) combined with two nucleoside reverse transcriptase inhibitors (NRTIs) [77].

Adverse side effects of anti-retroviral therapy

Twenty-one anti-HIV medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of AIDS. These medications must be given in combination, and all of the drugs may cause negative side effects ranging from mild to life-threatening. But, the adverse events associated with the therapy have been shown to compromise quality of life (QoL) and interfere with adherence to ARV regimens [78].

A. Hepatotoxicity: Hepatotoxicity is a term used for the liver damage. Hepatotoxicity has developed in HIV infected people who are administered with anti-HIV medications from three classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

There are several specific conditions that all fall within the general category of hepatotoxicity. These conditions include:

- Hepatitis—inflammation of the liver
- Hepatic necrosis—death of liver cells
- Hepatic steatosis—too much fat in the liver; may be associated with a life-threatening condition called lactic acidosis [79].

Nucleoside Reverse Transcriptase Inhibitors (NRTI)			
S.No	Drug	Common side effects	Adverse Side effects
1	Abacavir (Ziagen, ABC)	Hypersensitivity reactions (fever, skin rash), fatigue, etc.	Lactic acidosis; Lipodystrophy
2	Didanosine (Videx, dideoxyinosine, ddl)	Diarrhoea; nausea, vomiting, abdominal pain, fever, headache, rash	Peripheral neuropathy, Pancreatitis
3	Emtricitabine (Emtriva, FTC)	Diarrhoea; headache; nausea; rash	Hyperpigmentation; Hepatotoxicity; lactic acidosis
4	Lamivudine (Epivir, 3TC)	Nausea, vomiting, low fever, loss of appetite	Liver damage; lactic acidosis
5	Stavudine (Zerit, d4T)	Nausea, vomiting, Fever, rapid heart rate	Peripheral neuropathy, Genotoxic lipodystrophy
6	Tenofovir (Viread, TDF)	Nausea, vomiting, diarrhoea, asthenia	Acute renal failure, fanconi syndrome, Tubular necrosis
7	Zalcitabine (Hivid, ddC)	Nausea, headache	Peripheral neuropathy, Oral ulcers, Oesophageal ulcers, pancreatitis

Table 2: Side effects of NRTI drugs [54-61].

Protease Inhibitors (PI)			
S.No	Drug	Common side effects	Adverse side effects
1	Amprenavir (Agenerase, APV)	Gastrointestinal intolerance, rash, etc	Stevens-Johnson syndrome, hyperglycemia
2	Atazanavir (Reyataz, ATV)	Headache, nausea, skin rash	Hyperglycemia, asymptomatic hyperbilirubinemia, hyperlactatemia
3	Fosamprenavir (Lexiva, FOS)	Nausea, vomiting, diarrhoea	Kidney stones, Diabetes, hyperglycemia
4	Indinavir (Crixivan, IDV)	Fever, sore throat, headache, skin rash	Hyperbilirubinemia, nephrolithiasis, Urolithiasis
5	Lopinavir (Kaletra, LPV/r)	Loss of appetite, dark colored urine, abdominal pain	Jaundice, pancreatitis, hyperglycemia
6	Ritonavir (Norvir, RIT)	Loss of appetite, dark colored urine, abdominal pain	Hepatitis, pancreatitis, hyperglycemia
7	Saquinavir (Fortovase, Invirase, SQV)	Nausea, vomiting, diarrhoea	Hepatomegaly, Neutropenia

Table 3: Side effects of Protease inhibitors [62-68].

Fusion Inhibitors			
S.No	Drug	Common side effects	Adverse side effects
1	Enfuvirtide	Cough, insomnia, anorexia	Pneumonia, dyspnoea, arthralgia
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
1	Delavirdine (Rescriptor, DLV)	Fatigue, headache, nausea	Severe rash, liver toxicity
2	Efravirenz (Sustiva, EFV)	Dizziness, trouble sleeping,	Severe depression
3	Nevirapine (Viramune, NVP)	Mild/moderate rash	Stevens-Johnson syndrome, toxic epidermal necrosis, Hypersensitivity

Table 4: Side effects of Fusion inhibitors and NNRTIs [71-74].

Symptoms of hepatotoxicity: The signs and symptoms of hepatotoxicity fluctuate depending on how badly the liver is damaged. Symptoms of liver damage include nausea, vomiting, abdominal pain, loss of appetite, diarrhoea, feeling tired or weak, jaundice (yellowing of the skin and eyes), hepatomegaly (liver enlargement).

Cause: NRTIs, particularly Zerit (stavudine), Videx (didanosine), and Retrovir (zidovudine), are associated with lactic acidosis and hepatic steatosis [79].

B. Cardiovascular disease: Cardiovascular complications represent an increasingly essential health concern in HIV-infected population in particular after the commencement of anti-retroviral therapy. Numerous research studies have demonstrated the increased incidence of cardiovascular disease in HIV infected individuals. The stratification of cardiovascular risk in HIV patients poses a confront to the physicians in the modern age [79]. The first cardiac manifestation to be reported in AIDS patient was myocardial kaposi sarcoma on autopsy in 1983 [80].

This highly active anti retroviral treatment (HAART) schedule and the increased life span of infected individuals on HAART have led to an increased prevalence of cardiovascular complications, which were commonly unrecognized in the early days of the epidemic [81]. The use of combination antiretroviral therapy and atypical antipsychotic agents suggests worsening metabolic control in patients already at higher baseline cardiovascular risk [82].

Different types of diseases associated with cardiovascular manifestations are,

- **Pericardial disease:** Pericardial disease in AIDS can be symptomatic or asymptomatic; acute or chronic and can be attributed to various opportunistic infections or malignancies, but most of the times etiology is unidentified.
- **Myocardial disease:** Myocardial abnormalities occur in about 25-75% of patients infected with HIV, the wide range being attributed to patient risk factors, stage of disease and environmental factors [83].
- **Infective endocarditis:** Endocarditis in AIDS patients can be infective or nonbacterial e.g. marantic endocarditis. Infective endocarditis is responsible for about 5-20% of hospital admissions and about 5-10% of total deaths in HIV infected intravenous drug abusers [84].
- **Coronary artery disease:** HIV patients with CAD are known to have a histologically distinctive form of accelerated atherosclerosis, with diffuse and circumferential vessel involvement [85].

- **Systemic arterial hypertension:** The prevalence of systemic hypertension in HIV population is estimated to be about 20-25% before introduction of HAART. The Multicenter AIDS Cohort Study (MACS) showed a significantly higher systolic blood pressure in those using HAART for greater than five years [86].
- **Pulmonary hypertension:** HIV associated PAH is associated with decreased survival and a poorer prognosis as compared with HIV infected patients without this complication
- **Thrombosis & embolism:** HIV patients have an increased propensity to develop coagulation disorders. The mechanism is not clear. But it is attributed to increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1 [79].

C. Hyperglycemia: Despite significant improvements of the survival and quality of life style in HIV patients with the use of highly active antiretroviral therapy (HAART), cross-sectional and prospective studies have reported the onset of chronically complications including hyperlipidemia, lipodystrophy and impaired glucose metabolism, qualified as metabolic syndrome [87]. Hyperglycemia occurs when the person has a higher than usual level of glucose in his blood. This can happen shortly after a heavy meal and is not a problem if the glucose level returns to normal [88].

Symptoms: The most common symptoms of hyperglycemia include increased urination, excessive thirst or hunger, and unexplained weight loss.

Cause: Treatment with HIV protease inhibitors (PIs) and infection with hepatitis C virus enhance the risk of the onset of hyperglycemia and diabetes in people with HIV. The risk of developing hyperglycemia is about the same with all PIs [88].

D. Lactic Acidosis: Lactic acidosis is a physiological situation characterized by low pH in body tissues and blood (acidosis) accompanied by the buildup of lactate, in particular D-lactate, and is considered a distinct form of metabolic acidosis. The condition typically occurs when cells obtain very small amount of oxygen (hypoxia), for example during vigorous exercise. In this situation, impaired cellular respiration leads to lower pH levels. Simultaneously, cells are forced to metabolize glucose anaerobically, which leads to the production of lactate. Therefore, elevated lactate level is indicative of tissue hypoxia, hypoperfusion, and possible damage. Lactic acidosis is characterized by lactate levels >5 mmol/L and serum pH <7.35 [89].

Moderate to severe symptomatic hyperlactatemia and lactic acidosis are potentially life threatening and complicate the use of NRTIs. The development of lactic acidosis is one of the most grave mitochondrial toxicities with published case fatality rates of up to

80% among patients with lactate levels >10 mmol/L. Risk factors for the progress of moderate to severe symptomatic hyperlactatemia or lactic acidosis consist of female gender, use of “D” antiretroviral drugs (didanosine (ddI) and/or stavudine (d4T), possessing a BMI of >25, decreased CD4+ cell count, the presence of lipodystrophy, and having elevated plasma triglyceride levels [90].

Symptoms: The most common symptoms include Nausea, Vomiting, Hyperventilation (to remove CO₂), Abdominal pain, Lethargy, Anxiety, Severe anaemia, hypotension, irregular heart rate, Tachycardia [89].

Cause: Nucleoside reverse transcriptase inhibitors (NRTIs) can cause hyperlactatemia by disrupting the function of the mitochondria. This is known as mitochondrial toxicity. When the mitochondria don't work efficiently, excess lactate is produced [79].

E. Osteonecrosis, Osteopenia, and Osteoporosis:
Osteonecrosis: Osteonecrosis means “bone death.” Bone can undergo death if its blood supply is cut off and it fails to get nutrients; which is called avascular necrosis. Osteonecrosis occurs in the hip bones of some people with HIV, but doctors aren't sure why. It is unambiguous if osteonecrosis occurs due of HIV infection itself or as a side effect of the medications used to treat HIV.

Diagnosis: Diagnosis is best made by magnetic resonance imaging (MRI) of the bone. MRI is able to detect osteonecrosis before bone is significantly damaged and before abnormalities can be seen on an x-ray. X-rays and CT scans may also be used to look for osteonecrotic bone damage.

Symptoms: Symptoms of osteonecrosis comprise: pain in the affected area of the body; limited range of motion; joint stiffness; or limping; muscle spasms; progressive bone damage leading to bone collapse [79].

Osteopenia: Osteopenia is a state where bone mineral density is lower than usual. It is considered by many doctors to be a precursor to osteoporosis. However, not every person diagnosed with osteopenia will develop osteoporosis. More specifically, osteopenia is defined as a bone mineral density T-score between -1.0 and -2.5 [71].

Cause: Anyone can develop osteopenia and osteoporosis. You may be at increased risk if you take HIV protease inhibitors (PIs). You may also be at increased risk if you:

- Are female
- Take steroids or certain other medications
- Smoke
- Drink excessive amounts of alcohol
- Have low body weight [79].

Other side effects

• Natural killer (NK) cell function was investigated in Malaysian HIV patients beginning antiretroviral therapy (ART) with advanced immunodeficiency. Some patients experienced immune restoration disease (IRD) presenting as exacerbations of pre-existing infections [91].

- Immune Recovery Inflammatory Syndrome (IRIS) is characterized by a paradoxical deterioration of clinical status after commencement of Anti-Retroviral Therapy (ART),

in spite of improved immune function. It is caused by inflammatory response against the infectious antigen. IRIS typically occurs in patients with a low initial CD4 (usually <50) and a rapid decline in viral load [92].

- Patients infected with HIV typically seroconvert within weeks of primary HIV infection. In rare cases, patient do not develops antibodies despite demonstrable HIV infection by p24 antigen or viral load assays; a seronegative HIV. Very few such cases been reported so far in the literature [93].
- Use of some dideoxynucleotide analogues may be limited by mitochondrial toxicity leading to distal symmetric polyneuropathy (DSP) [94].
- It has been reported that patients who were administered with protease inhibitors (PIs)-based antiretroviral therapy (ART) show a higher HCV (Hepatitis C Virus) viremia than those treated with other regimens, mainly those including non-nucleoside reverse transcriptase inhibitors (NNRTI) [95].
- Some nucleoside retrotranscriptase inhibitors (NRTI) may reduce the tolerability of HCV therapy due to different interactions and toxicities, thereby reducing the rate of success of such a therapy. Thus, the administration of didanosine along with RBV is not recommended due to an increased risk of mitochondrial toxicity [96,98].

Conclusion

HIV-AIDS has gradually become pandemic affecting the entire world. Due to complexities in the HIV life cycle and structural changes which take place periodically, some of the current drug delivery systems intended to treat/prevent this disease turned out to be unsuccessful, ensuing minor to adverse side effects like Lactic Acidosis, Hepatotoxicity, Liver damage, Renal failure, Peripheral neuropathy, etc which are life threatening. Despite of these side effects, these medication procedures are proven to be highly efficient in combating the infection and thereby increasing the longevity of life in many HIV positive patients. Present review is mainly intended to alert people regarding the fact that few side effects and complications may be associated with the HAART therapy. More efficient drug delivery systems are needed for increased effective drug targeting and prevention of HIV-AIDS.

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